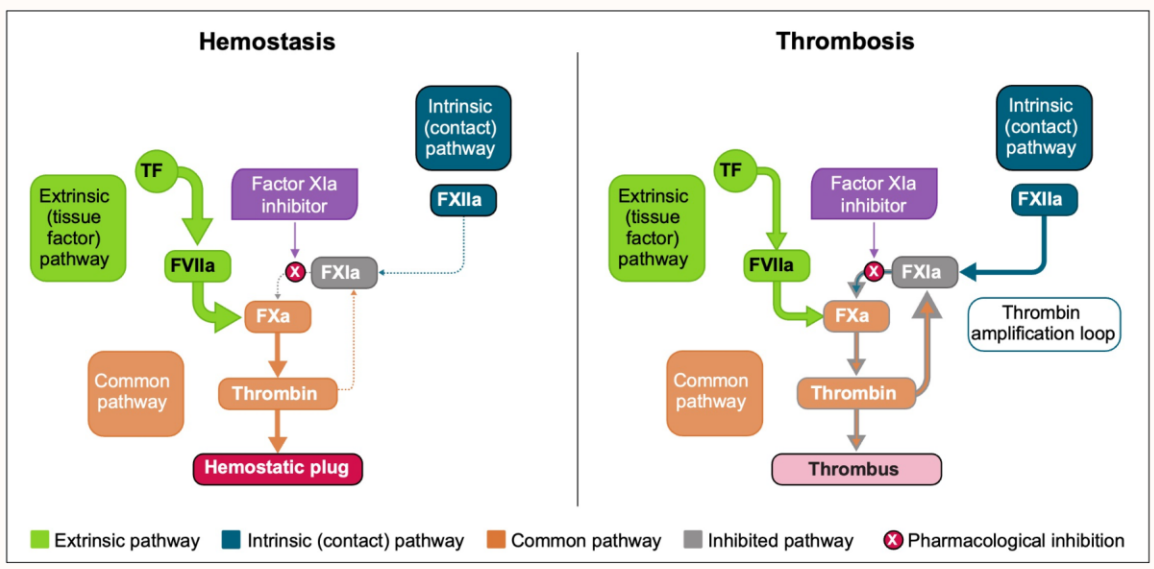
Factor XIa Inhibitors: A New Paradigm In Secondary Stroke Prevention

Secondary Stroke Prevention: Major unmet needs

- ~12 million strokes occur worldwide each year
- After ischemic stroke, recurrence affects ~1 in 10 survivors within 1 year and ~1 in 5 within 5 years
- Current secondary prevention strategies have only modestly reduced recurrence rates
- Bleeding risk with antiplatelet therapy complicates prevention in non-cardioembolic ischemic stroke and TIA
- The risk of secondary stroke immediately after a non-cardioembolic ischemic stroke/TIA remains unacceptably high, and persists for years afterwards, even with available secondary stroke prevention strategies
- There is a major unmet need for safer, more targeted antithrombotic therapies
- Mendelian randomization studies suggest genetically lower FXI levels are linked to lower ischemic stroke risk without increased major bleeding
- By inhibiting FXIa there is a potential to uncouple pathologic thrombosis from hemostasis.

Emerging New Paradigm: Factor XIa Inhibition in combination with antiplatelet therapy

Factor XIa inhibitors: uncouple hemostasis from thrombosis by preventing pathological thrombus formation without significant increase in major bleeding.

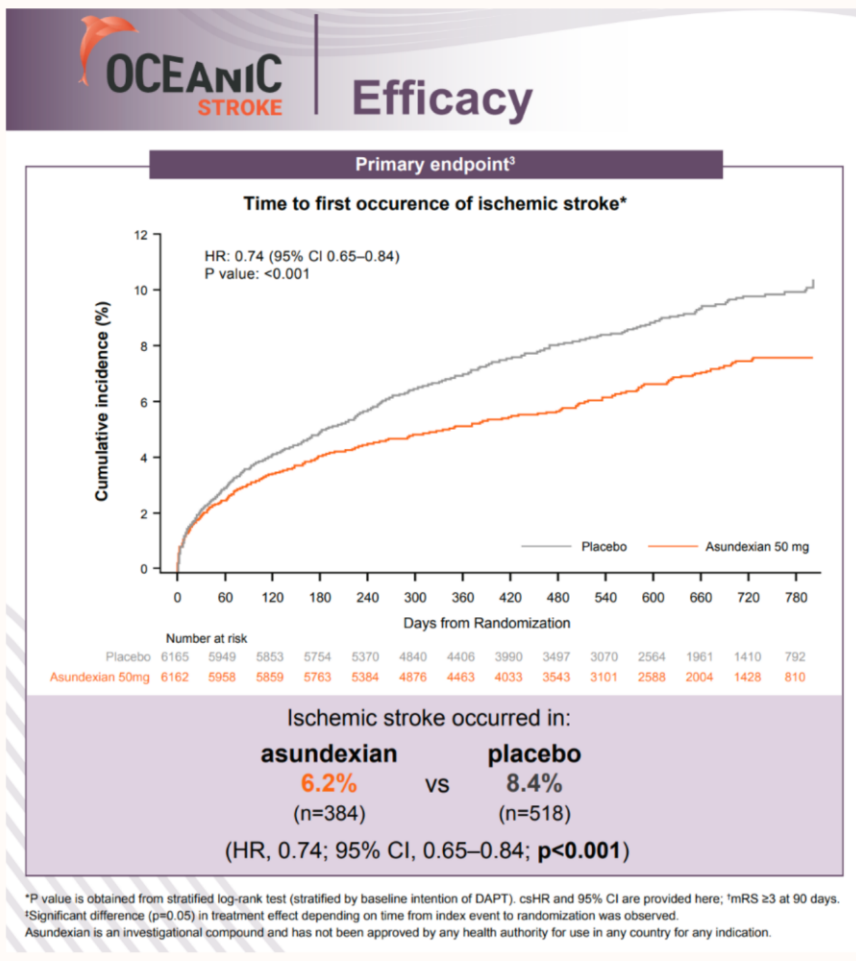


- Pathological thrombus growth occurs through activation of FXI to FXIa via thrombin and a positive feedback loop.
- FXIa role for hemostasis and formation of a hemostatic plug is minor due to being part of the intrinsic pathway.
- This mechanism applies irrespective of underlying atherosclerosis.

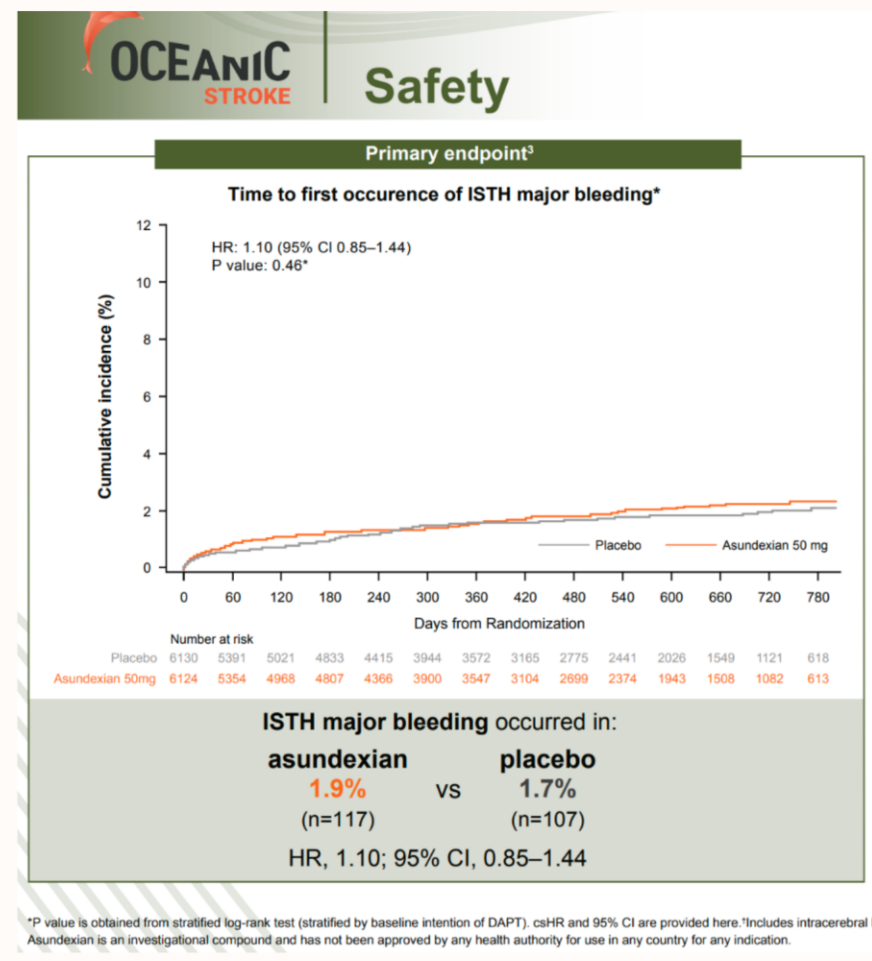
- Preclinical evidence & 2 Phase II studies indicate that FXIa inhibitors have the potential to prevent ischemic stroke without meaningful increase in bleeding.
- Asundexian (PACIFIC-STROKE) and milvexian (AXIOMATIC-SSP) were associated with numerically fewer ischemic strokes vs placebo.
- No increase in major bleeding with asundexian or milvexian vs placebo in combination with antiplatelet therapy.

Phase 3 studies: OCEANIC-STROKE and LIBREXIA-STROKE

There are two Phase III clinical trials investigating FXIa inhibiton in combination with APT after non-cardioembolic ischemic stroke or TIA in secondary stroke prevention, OCEANIC-STROKE demonstrating superiority to placebo, and ongoing LIBREXIA-STROKE.



*P value is obtained from stratified log-rank test (stratified by baseline intention of DAPT). csHR and 95% CI are provided here; †mRS ≥3 at 90 days.
‡Significant difference (p=0.05) in treatment effect depending on time from index event to randomization was observed.
Asundexian is an investigational compound and has not been approved by any health authority for use in any country for any indication.



*P value is obtained from stratified log-rank test (stratified by baseline intention of DAPT). csHR and 95% CI are provided here.†Includes intracerebral he
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- Asundexian 50 mg significantly reduced ischemic stroke by 26% (HR 0.74, 95% CI 0.65–0.84, P<0.001).
- A primary outcome event of ischemic stroke occurred in 384 (6.2%) patients assigned to asundexian and 518 (8.4%) patients assigned to placebo.
- Asundexian 50 mg once-daily in combination with antiplatelet therapy provided early, sustained, and consistent benefit across prespecified subgroups.

- There was no significant increase in the risk of ISTH major bleeding compared to placebo.
- Asundexian 50 mg once daily, in combination with antiplatelet therapy had similar rates of bleeding vs placebo across all secondary safety endpoints.

Key references:
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Piccini JP, et al. Lancet. 2022;399(10333):1383–90; Shoamanesh A, et al. Lancet. 2022;400(10357):997–1007; 6.
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